REMARKS

Claim Status

Claims 72, 74-79, 81-83, 85, 92, 96-99, 101-103, 105, 107, and 113-116 are pending in the application. Claims 85, 97, 98, 105, 113, and 115 have been amended to address minor grammatical errors and to clarify the claims. Claims 119 and 120 have been cancelled. The amendments are fully supported by the application as filed and do not add new matter.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 113-115 were rejected as allegedly indefinite. Specifically, the Examiner asserts that water and ethanol cannot be both solvents and nonsolvents. Applicants respectfully disagree.

As an initial matter, Applicants note that only claim 115 refers to ethanol or water as nonsolvents. Accordingly, there is no basis for including claims 113 and 114 in this rejection. The Examiner notes that claim 105 recites that the composition is prepared by hydrating or solubilizing the hyaluronic acid ester material in water, an organic solvent, or an aqueous buffer—i.e., a solvent, whereas claim 115 indicates that water is a nonsolvent.

It is well known that some substances are soluble in water and others are not. If a substance is soluble in water, then water is a solvent for that substance. Conversely, if a substance is not soluble in water, then water is a nonsolvent. The same is true, of course, for ethanol. Thus, the designation of either ethanol or water as a solvent or a non-solvent depends entirely on the substance that it is mixed with. In the claimed invention, ethanol or water may be suitable as solvents or nonsolvents depending on

the hyaluronic acid ester material used. This concept is clearly described in the specification at page 10. For example, a hydrophilic hyaluronic acid ester, such as Hyaff-11p65™ can be blended with an aqueous buffer. Alternatively, when using water insoluble hyaluronic acid esters, the gel formed in an organic solvent is extruded into a nonsolvent, e.g., water or ethanol, enabling precipitation of the material. This point is further illustrated at page 20 of the specification, which describes an embodiment of the invention where Hyaff-11™ is mixed in an organic solvent and then extruded into ethanol as a nonsolvent.

Thus, one of skill in the art will readily understand that ethanol and water can act as solvents or nonsolvents depending on the hyaluronic acid ester material used when practicing the invention. However, in an effort to facilitate prosecution, Applicants have amended claim 115 to make this distinction more clear. Accordingly, Applicants submit that claims 113-115 comply with 35 U.S.C. § 112, second paragraph, and request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102(b)

Claims 72, 74-75, 85, and 92 stand rejected as allegedly anticipated by WO 01/28602. The Examiner alleges that this PCT publication discloses injectable formulations comprising a pharmaceutical admixture of osteogenic protein, hyaluronic acid derivative, and tricalcium phosphate to form porous injectable gels and pastes. The Examiner acknowledges that WO 01/28602 does not specifically disclose that the composition is in the form of a solid rod but asserts that by extruding the disclosed

composition through a needle, it would necessarily be in rod form. Applicants respectfully traverse.

In making this rejection under 35 U.S.C. §102, the Examiner has completely ignored the clear distinction between WO 01/28602 and Applicants' invention, i.e., Applicants' composition is a solid. The claims specify that the hyaluronic acid ester and osteogenic protein mixture are "in the form of a cylindrical rod suitable for intraosseous injection in *solid state*..." That is, the claimed rod is solid before injection, not after injection. WO 01/28602 makes clear that when its compositions undergo precipitation/phase inversion of the carrier, it takes place *in situ*, i.e., after injection. (See page 3). Thus, when the compositions disclosed in WO 01/28602 are injected through a needle, they are not in the solid state required by Applicants' claims.

Moreover, the Examiner has provided no reasonable scientific basis to believe, nor does WO 01/28602 ever suggest, that its gels and pastes would be in rod shape even after injection. The formulations in WO 01/28602 were selected to be injectable through an 18 gauge needle (see page 7, line 10), which has an inner diameter of less than 1 mm ($1/30^{th}$ of an inch; see attached needle gauge chart). Once extruded under pressure through this narrow bore and into bone, the composition will encounter spongy bone, marrow, and connective tissue and lose any shape that it may have had. As the attached definitions of "bone" and "marrow" make clear, the interior of the bone is not a hollow cavity but is filled with a highly cellular hematopoietic connective tissue. Thus, one of skill in the art would believe that the cited compositions would deform upon meeting resistance at the injection site and then partially solidify into an amorphous shaped porous scaffold.

Accordingly, WO 01/28602 does not disclose all elements of Applicants' claims and does not anticipate them. Withdrawal of the rejection and reconsideration of the claims are courteously solicited.

Rejections Under 35 U.S.C. § 103

Claims 72, 74-75, 85, and 92 stand rejected as allegedly obvious in view of WO 01/28602. Again, the Examiner asserts that the compositions disclosed in WO 01/28602 differ from those claimed by Applicants only in that there is no specific teaching that they are in the form of a solid [cylindrical] rod. The Examiner believes that they would inherently be in rod shape after extrusion through a needle. Applicants respectfully traverse.

As discussed above, WO 01/28602 does not teach or suggest that its compositions are in the form of a solid cylindrical rod *before* injection or that they would be in rod shape even after injection. In addition, pages 8-9 of the specification detail numerous advantages of the claimed solid rods over liquid or gel/paste formulations including:

- the claimed solid rod compositions avoid premature dilution of the osteoinductive agent by bodily fluids, thus providing a sustained release of osteogenic factor;
- the claimed solid rod compositions considerably mitigate the risk of embolism during intraosseous injection due, in part, to the reduced volume of the highly concentrated solid rod that must be injected to facilitate bone growth; and
- the claimed solid rod compositions become lodged and persist at the site of desired bone growth rather than migrating away from the desired site.

Applicants respectfully aver that the present invention and WO 01/28602 simply disclose distinct formulations with distinct physical and biological properties, each suitable for particular applications. The claimed compositions and those of WO 01/28602 are in no way obvious variants of each other. Applicants Kim and Li are also the first named inventors on WO 01/28602 and thus, were intimately familiar with its teachings during development of the present invention. The claimed invention is based, in part, on the numerous advantages of the claimed solid rods over the cited paste/gel formulations, already discussed above. Applicants respectfully submit that that for these reasons WO 01/28602 fails to render the present claims obvious and request that the rejection be withdrawn.

The Examiner further rejects all pending claims as allegedly obvious over WO 01/28602, in view of Vercruysee, et al., *Critical Review in Therapeutic Drug Carrier Systems* 15:513-55 (1998); Campoccia et al., *Biomaterials* 19: 2101-27 (1998) (for disclosing, along with Vercruysee et al., that hyaluronic acid esters can be cross-linked); and U.S. Patent Nos. 6,221,958 (for disclosing specific dimensions of a polyester paste extruded through an 18 gauge needle) and 6,015,801 (for disclosing the use of bisphosphonates to limit bone resorption). Applicants respectfully traverse.

None of these references, alone or in combination, remedy the deficiencies of WO 01/28602, discussed above. Their collective disclosures fail to offer any teaching, suggestion, or motivation to make the compositions of WO 01/28602 in the form of a solid cylindrical rod suitable for intraosseous injection. Consequently, none of these references, alone or in combination, render the instant claims obvious. Withdrawal of the rejections and reconsideration of the pending claims are courteously solicited.

Rejections Under 35 U.S.C. § 101 and Obviousness-Type Double Patenting

Claims 72, 74, 85, 92, 99, 105, 107, 113, and 116 stand rejected under 35 U.S.C. § 101 as allegedly unpatentable over claims 1, 3, 9, 11, 14, 15, 17, 19, and 25-27 of U.S. Patent No. 7,189,392, the US counterpart to WO 01/28602, discussed above. The same claims stand rejected for non-statutory obviousness-type double patenting over the '392 patent, further in view of the '958 patent (disclosing the use of polyester pastes), also discussed *supra*. Applicants respectfully traverse.

As discussed under the 35 U.S.C. § 102 and 103 rejections for WO 01/28602, the '392 patent does not anticipate or render obvious a composition comprising a hyaluronic acid ester and osteogenic protein in the form of a cylindrical rod suitable for intraosseous injection in the solid state into a body. The '958 patent does not remedy these deficiencies. Accordingly, Applicants respectfully request withdrawal of the rejections and reconsideration of the pending claims.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: June 11, 2008

By: _____

Laurence A. Shumway, Ph.D.
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Attachments:

- Sigma-Aldrich Co., Needle Conversion Chart, http://www.sigmaaldrich.com/Area_of_Interest/Research_Essentials/Chemicals/Key_Resources/Technical_Library/Needle_Gauge_Chart.html, screenshot dated 05/07/08;
- Stedman's Medical Dictionary p. 223 "bone" (27th ed. 2000);
- Stedman's Medical Dictionary p. 1067 "marrow" (27th ed. 2000).

Syringe Needle Conversion Chart

Needle		Nominal O.D.		Nominal I.D.		
Gauge	*mm*	*inches*	*tol. (in.)*	*mm*	*inches*	*tol. (in.)*
10	3.404	0.1340	±0.0010	2.692	0.1060	±0.0020
11	3.048	0.1200	"	2.388	0.0940	"
12	2.769	0.1090	"	2.159	0.0850	"
13	2.413	0.0950	"	1.803	0.0710	"
14	2.108	0.0830	"	1.600	0.0630	"
15	1.829	0.0720	±0.0005	1.372	0.0540	±0.0015
16	1.651	0.0650	"	1.194	0.0470	"
17	1.473	0.0580	"	1.067	0.0420	"
18	1.270	0.0500	"	0.838	0.0330	"
19	1.067	0.0420	"	0.686	0.0270	"
20	0.902	0.0355	+0.0005 -0.0000	0.584	0.0230	+0.0015 -0.0000
21	0.813	0.0320	"	0.495	0.0195	"
22	0.711	0.0280	"	0.394	0.0155	"
22s	0.711	0.0280	"	0.140	0.0055	"
23	0.635	0.0250	"	0.318	0.0125	"
24	0.559	0.0220	"	0.292	0.0115	"
25	0.508	0.0200	"	0.241	0.0095	"
25s	0.508	0.0200	"	0.140	0.0055	"
26	0.457	0.0180	"	0.241	0.0095	"
26s	0.467	0.0184	"	0.114	0.0045	"
27	0.406	0.0160	"	0.191	0.0075	"
28	0.356	0.0140	"	0.165	0.0065	"
29	0.330	0.0130	"	0.165	0.0065	"
30	0.305	0.0120	"	0.140	0.0055	"
31	0.254	0.0100	"	0.114	0.0045	"
32	0.229	0.0090	"	0.089	0.0035	"
33	0.203	0.0080	"	0.089	0.0035	"

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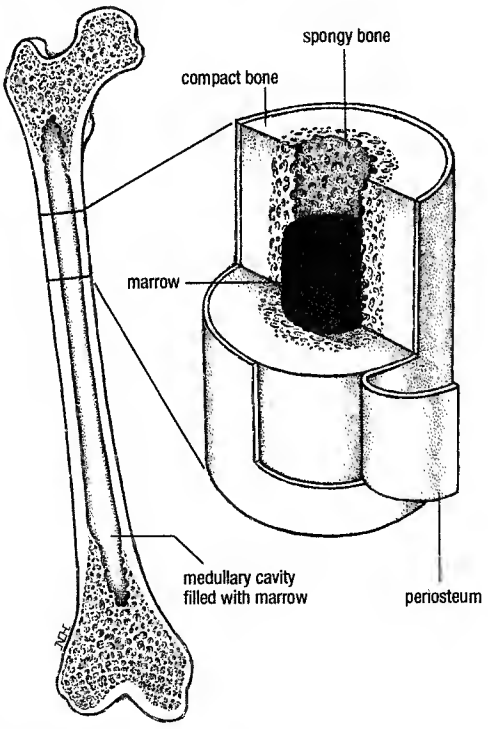
attachment, such as between parent and child, lovers, or husband and wife.

BONE

bone (bōn) [TA]. A hard connective tissue consisting of cells embedded in a matrix of mineralized ground substance and collagen fibers. The fibers are impregnated with a form of calcium phosphate similar to hydroxyapatite as well as with substantial quantities of carbonate, citrate sodium, and magnesium; by weight, b. is composed of 75% inorganic material and 25% organic material; a portion of osseous tissue of definite shape and size, forming a part of the animal skeleton; in humans there are 200 distinct b.'s in the skeleton, not including the auditory ossicles of the tympanic cavity or the sesamoid b.'s other than the two patellae. Bone consists of a dense outer layer of compact substance or cortical substance covered by the periosteum, and an inner loose, spongy substance; the central portion of a long bone is filled with marrow. SYN os [TA]. [A.S. *bān*]



bone

Albrecht b., a small b. between the basioccipital and basisphenoid.

alveolar b., (1) SYN alveolar *process* of maxilla; **(2)** in dentistry, the specialized bony structure which supports the teeth; it consists of the cortical b. that comprises the tooth socket into which the roots of the tooth fit, and is supported by the trabecular b. SYN alveolar supporting b.

alveolar supporting b., SYN alveolar b., (2).

ankle b., SYN talus.

arm b., SYN humerus.

basal b., the osseus tissue of the mandible and maxillae except the alveolar processes.

basilar b., the developmental basilar process of the occipital b. that unites with the condylar portions in about the fourth or fifth year, becoming the basilar *part* of occipital bone. SEE ALSO basilar *part* of occipital bone. SYN basioccipital b., os basilare.

basioccipital b., SYN basilar b.

basisphenoid b., in comparative anatomy, the b. in the floor of the brain case in the region of the pituitary. SEE *body* of sphenoid.

Bertin b.'s, SYN sphenoidal *conchae*, under *concha*.

blade b., SYN scapula.

breast b., SYN sternum.

Breschet b.'s, SYN suprasternal b.'s.

brittle b.'s, SYN *osteogenesis* imperfecta.

bundle b., immature b. containing thick bundles of collagen fibers arranged nearly parallel to one another with osteocytes in between; a similar type of b. is found in regions penetrated by fibers of Sharpey, as at ligament and tendon attachments.

calcaneal b., SYN calcaneus (1).

calf b., SYN fibula. [O.N. *kalfi*, fibula]

cancellous b., SYN *substantia* spongiosa.

capitate b., SYN capitate (1).

carpal b.'s [TA], eight b.'s arranged in two rows that articulate proximally with the radius and indirectly with the ulna, and distally with the five metacarpal b.'s; in domestic mammals, the b.'s of the proximal row are called radial, intermediate, ulnar, and accessory, while those of the distal row are termed first, second, third, and fourth carpal b.'s. SYN carpus (2) [TA], ossa carpi [TA].

cartilage b., SYN endochondral b.

central b., SYN *os* centrale.

central b. of ankle, SYN navicular.

cheek b., (1) SYN zygomatic b; **(2)** SYN zygomatic *arch*.

coccygeal b., SYN coccyx.

collar b., SYN clavicle.

compact b. [TA], the compact, noncancellous portion of b. that consists largely of concentric lamellar osteons and interstitial lamellae. SYN substantia compacta [TA], compact substance, substantia compacta ossium.

convoluted b., SEE inferior nasal *concha*, middle nasal *concha*, superior nasal *concha*, supreme nasal *concha*.

cortical b. [TA], the superficial thin layer of compact b. SYN substantia corticalis [TA], cortical substance.

coxal b., ☆official alternate term for hip b.

cranial b.'s, SYN b.'s of cranium.

b.'s of cranium [TA], the paired inferior nasal concha, lacrimal, maxilla, nasal, palatine, parietal, temporal, and zygomatic; and the unpaired ethmoid, frontal, occipital, sphenoid, and vomer. SYN ossa cranii [TA], b.'s of skull, cranial b.'s.

cubital b., SYN triquetrum.

cuboid (b.), the lateral b. of the distal row of the tarsus, articulating with the calcaneus, lateral cuneiform, navicular (occasionally), and fourth and fifth metatarsal b.'s. SYN os cuboideum.

cuneiform b., SEE triquetrum, intermediate cuneiform (b.), lateral cuneiform (b.), medial cuneiform (b.).

dermal b., a b. formed by ossification of the cutis.

b.'s of digits, the phalanges and sesamoid b.'s of the fingers and toes. SYN ossa digitorum☆.

dorsal talonavicular b., an anomalous b. of the foot located near the head of the talus. SYN Pirie b.

ear b.'s, SYN auditory *ossicles*, under *ossicle*.

elbow b., SYN olecranon.

endochondral b., a b. that develops in a cartilage environment after the latter is partially or entirely destroyed by calcification and subsequent resorption. SYN cartilage b., replacement b.

epactal b.'s, SYN sutural b.'s.

epihyal b., an ossified stylomastoid ligament.

epipteric b., a sutural b. occasionally present at the pterion or junction of the parietal, frontal, greater wing of the sphenoid, and squamous portion of the temporal b.'s. SYN Flower b.

episternal b., SYN suprasternal b.'s.

ethmoid b. [TA], an irregularly shaped b. lying between the orbital plates of the frontal and anterior to the sphenoid b.; it consists of two lateral masses of thin plates enclosing air cells, attached above to a perforated horizontal lamina, the cribriform

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mar·i·no·bu·fo·tox·in (mar'i-nō-boo'fō-toks-in). A poison produced by the parotid gland of *Bufo marinus* (family Bufonidae), a large toad native to Central and South America; used in tropical countries for insect control.

Marion, Georges, French urologist, 1869–1932. SEE M. *disease.*

Mariotte, Edmé, French physicist, 1620–1684. SEE M. *bottle, experiment, law,* blind *spot.*

mar·i·po·sia (mār-i-pō'zē-ă). Thallasoposia; rarely used term for abnormal consumption of sea water as a result of psychogenic factors. SYN thalassoposia. [L. *mare,* the sea, + G. *posis,* drinking]

Marjolin, Jean N., French physician, 1780–1850. SEE M. *ulcer.*

mar·jo·ram (mar'jō-ram). Sweet, leaf, or garden m. whose leaves, with and without a small portion of the flowering tops of *Majorana hortensis* (*Origanum majorana*) (family Labiatae), are used as seasoning and medicinally as a stimulant, carminative, and emmenagogue.

mark. **1.** Any spot, line, or other figure on the cutaneous or mucocutaneous surface, visible through difference in color, elevation, or other peculiarity. [A.S. *mearc*]

alignment m., m.'s made in tracings while the kymograph or other recording apparatus is at rest in order to indicate the time relations between two tracings inscribed one above the other, e.g., jugular and radial pulses.

stretch m.'s, SYN *striae* cutis distensae, under *stria.*

mark·er. **1.** A device used to make a mark or to indicate measurement. **2.** A characteristic or factor by which a cell or molecule can be recognized or identified. **3.** A locus containing two or more alleles that, being harmless, are common and therefore yield high frequencies of heterozygotes which facilitate linkage *analysis.*

allotypic m., SYN allotype.

cell m., an identifying characteristic of a cell; e.g., formation of rosettes with sheep erythrocytes as a m. of T lymphocytes, or the presence of surface immunoglobulin as a m. of B lymphocytes.

cell surface m., a surface protein, glycoprotein, or group of proteins that distinguish a cell or subset of cells from another defined subset of cells.

genetic m., SYN genetic *determinant.*

linkage m., a locus at which there is a high probability of heterozygotes (indispensible state for linkage analysis), but in itself perhaps of no clinical interest. SEE ALSO marker *locus.*

oncofetal m., a tumor m. produced by tumor tissue and by fetal tissue of the same type as the tumor, but not by normal adult tissue from which the tumor arises.

polymorphic genetic m., inherited characteristic that occurs within a given population as two or more traits.

time m., an instrument that marks the time, usually in seconds or fractions of seconds, on a kymograph record in physiologic experiments.

tumor m., a substance, released into the circulation by tumor tissue, whose detection in the serum indicates the presence of tumor.

tumor markers used in primary diagnoses

type of tumor	marker
testicular carcinoma, choriocarcinoma	β-subunit of human choriogonadotropin (β-HCG) and α-1-fetoprotein (AFP)
multiple myeloma	immunoglobulins, Bence Jones protein
neuroblastoma, pheochromocytoma	catecholamines, vanillylmandelic acid, metanephrines
carcinoid, primary liver-cell carcinoma	5-hydroxyindoleacetic acid α-1-fetoprotein
medullary thyroid gland carcinoma	calcitonin
malignant lymphoma, leukemia	surface antigens

Markov, Andrei, Russian mathematician, 1865–1922. SEE Markov *process.*

Marme re·a·gent. See under reagent.

mar·mo·rat·ed (mar'mō-rā-ted). Denoting a condition in which the appearance of the skin is streaked like marble. SEE ALSO *cutis* marmorata. [L. *marmoratus,* marbled]

mar·mot (mar'mot). A woodchuck or groundhog; a hibernating rodent that may serve as reservoir host of plague bacillus in North America. [Fr. *marmotte*]

Maroteaux, Pierre, French medical geneticist, *1926. SEE M.-Lamy *syndrome.*

Marquis re·a·gent. See under reagent.

mar·row (mar'ō) [TA]. **1.** A highly cellular hematopoietic connective tissue filling the medullary cavities and spongy epiphyses of bones; it becomes predominantly fatty with age, particularly in the long bones of the limbs. **2.** Any soft gelatinous or fatty material resembling the m. of bone. SEE ALSO medulla. [A.S. *mearh*]

bone m. [TA], the soft, pulpy tissue filling the medullary cavities of bones, having a stroma of reticular fibers and cells; it differs in consistency by age and location. SEE ALSO gelatinous bone m., red bone m., yellow bone m. SYN medulla ossium [TA].

gelatinous bone m. [TA], degenerated marrow of cranial bones in old age.

red bone m. [TA], bone marrow in which the stroma primarily contain the developmental stages of erythrocytes, leukocytes, and megakaryocytes; it is present throughout the skeleton during fetal life and at birth. After the fifth postnatal year, it is gradually replaced in the long bones by yellow marrow. SYN medulla ossium rubra [TA].

spinal m., SYN spinal *cord.*

yellow bone m. [TA], bone m. in which the stroma of the reticular network are largely filled primarily with fat; it replaces red marrow in the long bones after the fifth year of life. SYN medulla ossium flava [TA].

Marshall, Don, U.S. ophthalmologist, *1905. SEE M. *syndrome.*

Marshall, Eli K., U.S. pharmacologist, 1889–1966. SEE M. *method.*

Marshall, John, English anatomist, 1818–1891. SEE M. vestigial *fold,* oblique *vein.*

Marshall, Victor F., U.S. urologist, *1913. SEE M. *test;* M.-Marchetti *test;* M.-Marchetti-Krantz *operation.*

Mar·shal·la·gia mar·shalli (mar-sha-lā'jē-ă mar-shal'ī). One of the medium stomach worms of the nematode family Trichostrongylidae, found in the abomasum of sheep, goats, camels, and various wild ruminants.

marsh·mal·low root (marsh'mal-ō). SYN althea.

mar·su·pi·al (mar-soo'pē-ăl). **1.** A member of the order Marsupalia, which includes such mammals as kangaroos, wombats, bandicoots, and opossums, the female of which has an abdominal pouch for carrying the young. **2.** Of or pertaining to marsupials. [L. *marsupium,* a pouch]

mar·su·pi·al·i·za·tion (mar-soo'pē-ăl-i-zā'shŭn). Exteriorization of a cyst or other such enclosed cavity by resecting the anterior wall and suturing the cut edges of the remaining wall to adjacent edges of the skin, thereby creating a pouch. [L. *marsupium,* pouch]

mar·su·pi·um (mar-soo'pē-ŭm). **1.** SYN scrotum. **2.** A pouch or sac; e.g., in marsupials. [L. pouch]

Martegiani, J., 19th century Italian anatomist. SEE M. *area, funnel.*

Martin, August E., German gynecologist, 1847–1933. SEE M. *tube;* M.-Gruber *anastomosis.*

Martin, Henry A., U.S. surgeon, 1824–1884. SEE M. *bandage, disease.*

Martin, J.E. SEE Thayer-M. *medium.*

Martinotti, Giovanni, Italian physician, 1857–1928. SEE M. *cell.*

mar·ti·us yel·low (marsh'ē-ŭs) [C.I. 10315]. An acid dye used as a stain in plant and animal histology, and as a light filter for photomicrography. [Karl A. *Martius,* Ger. chemist, *1920]

ma